Potential new therapy relieves chronic itch

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MD/PhD student Landon K. Oetjen (left) and Brian S. Kim, MD (center), examine chronic itch patient Donald E. Hodges, whose symptoms improved following treatment with the arthritis drug tofacitinib. Kim and Oetjen tested the strategy in Hodges and four others after mouse studies suggested it might interfere with a pathway through which immune system molecules act directly on nerve cells to make people feel itchy. Credit: Karen Elshout

The roots of chronic itching have long remained a mystery. Meanwhile, those with the condition suffer from an unrelenting and sometimes debilitating urge to scratch. Now, new research at Washington University School of Medicine in St. Louis has identified immune signaling molecules that are essential for activating neurons in the skin to cause chronic itching.

In a small study, the researchers also discovered that people with a type of itch from an unknown cause, a condition called chronic idiopathic pruritus, improve when given tofacitinib (Xeljanz), a drug approved for rheumatoid arthritis. Earlier attempts to treat their itching with other anti-inflammatory drugs had not been successful, but within one month of taking tofacitinib, all five patients in the study experienced marked relief from severe itching.

The findings are published Sept. 8 in the journal *Cell*.

"These patients often itch day and night, and for some of them, the urge to scratch never goes away," said senior investigator Brian S. Kim, MD, an assistant professor of medicine and co-director of Washington University's Center for the Study of Itch. "Although this was a small study, the patients taking tofacitinib experienced dramatic improvements in terms of their itch, allowing them to sleep, stop scratching and return to living more productive lives. Obviously, we'll need to do a larger study, but the early results are very encouraging."

The findings also explain why an earlier study found that itching dissipates dramatically in eczema patients treated with the new drug dupilumab (Dupixent). Eczema patients have itchy, scaly rashes. The Washington University researchers found that drugs such as tofacitinib and dupilumab work so well, where many other drugs have failed, because they act directly on the nerves rather than only on the immune system.

Chronic itch affects up to 15 percent of the population and is most often caused by inflammatory conditions such as eczema and psoriasis but also is associated with kidney failure, liver disease and certain cancers and nerve disorders. However, cases of chronic itching for which there are no known causes are particularly puzzling and among the most difficult to treat.

As part of the study, the researchers showed that sensory neurons in mice and people are activated by the immune signaling molecule called interleukin-4 (IL-4).

"We found a link between the immune system and the nervous system that wasn't previously appreciated, showing that this immune molecule directly stimulates nerve cells to cause itching," Kim said.

Further, the researchers showed that IL-4 signaling can jump-start chronic itching in the setting of inflammation but also independently of pathways directly linked to inflammation. Chronic idiopathic pruritus, for example, isn't associated with inflammation, which is why anti-inflammatory treatments, such as steroid creams, are ineffective.

Kim's team, led by MD/PhD student and first author Landon K. Oetjen, also engineered mice to have sensory neurons that lacked the ability to respond to IL-4. When these mice were exposed to stimuli that should have made them itch, they didn't scratch. These findings may help explain why the new drug dupilumab has had such remarkable success in improving itch in patients with eczema.

The researchers then determined that IL-4 stimulates a key protein within nerve cells – JAK1 – that is a critical component of chronic itching. That finding led the team to suspect that JAK1 may be a uniquely sensitive target for multiple types of itch, even itching of unknown cause. The existing arthritis drug tofacitinib blocks this

protein, so several of Kim's patients with chronic idiopathic pruritus were given the drug.

"We didn't know if tofacitinib would work in patients with chronic idiopathic pruritus, but our studies in mice suggested it might," Kim said.

Although the patients with chronic idiopathic pruritus usually didn't have rashes on their skin, they still had severe and debilitating itch. But when taking tofacitinib, those patients experienced, on average, almost an 80 percent improvement in their itch severity.

"It's a rare situation where our mouse studies precisely predict what we're seeing in human patients," Kim said. "Next, we want to carry out larger studies in patients with chronic itch to evaluate whether tofacitinib can be modified to eliminate itching without also interfering with the patients' immune systems."

More information: Landon K. Oetjen et al. Sensory Neurons Co-opt Classical Immune Signaling Pathways to Mediate Chronic Itch, *Cell* (2017). DOI: 10.1016/j.cell.2017.08.006

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